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Implementing a care bundle approach reduces ventilator-associated pneumonia and delays ventilator-associated tracheobronchitis in children: differences according to endotracheal or tracheostomy devices

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SUMMARY

Objective: To reduce ventilator-associated infections (VARI) and improve outcomes for children.
Methods: This prospective interventional cohort study was conducted in a paediatric intensive care unit (PICU) over three periods: pre-intervention, early post-intervention, and late post-intervention. These children were on mechanical ventilation (MV) for ≥48 h.
Results: Overall, 312 children (11.9% of whom underwent tracheostomy) and 6187 ventilator-days were assessed. There was a significant reduction in ventilator-associated pneumonia (VAP) among tracheostomized patients (8.16, 3.27, and 0.65 per 1000 tracheostomy ventilation-days before the intervention, after the general bundle implementation, and after the tracheostomy intervention, respectively). The median time from onset of MV to diagnosis of ventilator-associated tracheobronchitis (VAT) increased from 5.5 to 48 days in the late post-intervention period ($p = 0.004$), and was associated with a significant increase in median 28-day ventilator-free days and PICU-free days. Tracheostomy (odds ratio 7.44) and prolonged MV (odds ratio 2.75) were independent variables significantly associated with VARI. A trend towards a reduction in PICU mortality was observed, from 28.4% to 16.6% (relative risk 0.58).
Conclusions: The implementation of a care bundle to prevent VARI in children had a different impact on VAP and VAT, diminishing VAP rates and delaying VAT onset, resulting in reduced healthcare resource use. Tracheostomized children were at increased risk of VARI, but preventive measures had a greater impact on them.

1. Introduction

There has been growing interest in bringing down the rates of ventilator-associated pneumonia (VAP) by applying the successful multi-disciplinary approach for reducing central line-associated bloodstream infections in intensive care units (ICUs).[1,2] However, as noted by Shahin et al.,[3] most studies aimed at achieving a zero VAP rate have excluded high-risk patients such as immunocompromised patients, patients already treated with antibiotics, and patients on prolonged mechanical ventilation – even though the latter are the most resource-intensive recipients of critical care, and their morbidity and mortality rates are high.[4] Ventilator-associated tracheobronchitis (VAT) has also been independently associated with adverse outcomes and has been identified as an important source of PICU morbidity: it may in fact be more prevalent than VAP in children and is likely to be a clinically important nosocomial infection in its own right.[5,6] Muszynski et al. reported successful implementation of a care bundle to prevent VAT in a paediatric ICU (PICU).[7] However, it appears that the simultaneous impact of the implementation of a ventilator care bundle on VAP and VAT rates has not yet been assessed in children, including patients undergoing prolonged mechanical ventilation.

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Furthermore, the role of tracheostomy as a risk factor for VAP or VAT in children has not been assessed either, since tracheostomy for children admitted to the PICU is infrequent, related to previous prolonged mechanical ventilation at home or performed late following PICU admission, usually surgical.[8]

It was hypothesized that VAP and VAT are different. The primary objective of this study was to evaluate whether the implementation of a ventilator care bundle in the PICU could simultaneously reduce the incidence of VAP and VAT in critically ill children, including those on prolonged mechanical ventilation. The primary outcome was the reduction in VAP and VAT rates, taking into account the two airway devices (endotracheal and tracheostomy tubes); the secondary outcome measures were ventilator-free days, PICU-free days, and PICU mortality.

2. Materials and methods

2.1. Study design and setting

A prospective, pre- and post-intervention cohort study was conducted in a 16-bed medical–surgical PICU of a 220-bed tertiary care paediatric hospital, which serves as a referral centre for transplant, burns, haemato-oncological, and immunocompromised children, admitting patients from 1 week to 16 years of age.

The study was divided into three periods: (1) the pre-intervention period (PI), from January 2010 to December 2010; (2) the early post-intervention period (EP), from January 2011 to December 2011; (3) the late post-intervention period (LP), from January 2012 to December 2012.

2.2. Data collection and definitions

All children admitted to the PICU who had received invasive mechanical ventilation (MV) for 48 h or longer were included. There were no exclusion criteria. Cases of VAP or VAT were recorded according to the US Centers for Disease Control and Prevention (CDC) criteria.[9,10] In brief, VAP was defined as the presence of a new or progressive and persistent pulmonary infiltrate, consolidation, or cavitation (or pneumatoceles in those aged ≤1 year) and at least three of the following, in a patient under MV for ≥48 h:[9] (1) temperature >38 °C or <36.5 °C with no other recognized cause; (2) leukocyte count $\geq 12 \times 10^9$/l (15×10^9/l for ≤12 years old) or $<4 \times 10^9$/l ; (3) new onset of purulent tracheal secretions or change in character of sputum, or increased respiratory secretions or increased suctioning requirements; (4) new onset or worsening cough, or dyspnoea, apnoea, or tachypnoea; (5) wheezing, rales, or bronchial breath sounds; (6) worsening gas exchange, increased oxygen requirements, or increased ventilator demand (mandatory point for infants ≤1 year old); and (7) bradycardia (<100 beats/min) or tachycardia (>170 beats/min) (only for infants ≤1 year old). The diagnosis of VAP was considered to be laboratory-confirmed if either bronchoalveolar lavage or endotracheal aspirate cultures presented significant growth ($>10^4$ CFU or $>10^5$ CFU, respectively). VAT was defined on the basis of the absence of clinical and radiographic evidence of pneumonia, the presence of a positive culture obtained by deep tracheal aspirate, and at least two of the following signs in a patient under MV for ≥48 h:[9] fever >38 °C, cough, new or increased purulent tracheal secretions, rhonchi, and wheezing (and/or respiratory distress, apnoea, or bradycardia in infants ≤1 year old). Ventilator-associated respiratory infection (VARI) included VAP and VAT cases, as defined elsewhere.[11] The incidence rates of VAP, VAT, and VARI were expressed as the cases of VAP, VAT, and VARI per 1000 ventilator-days. Tracheostomy and endotracheal VAP, VAT, and VARI incidence rates were also calculated, defined as cases of VAP, VAT, and VARI per 1000 tracheostomy-days on MV (tracheostomy ventilator-days) or endotracheal tube ventilator-days, respectively.

Clinical and demographic information, including the Paediatric Logistic Organ Dysfunction (PELOD) score,[12] duration of MV, length of stay, ventilator- and PICU-free days, and mortality were recorded. Prolonged mechanical ventilation (PMV) was defined as the need for ≥21 consecutive days of MV for ≥6 h per day.[13]

This study was performed as part of the surveillance programme for the prevention and control of nosocomial infections at the authors' centre. The need for individual informed consent is waived for the practice of surveillance, prevention, and infection control activities. The study was conducted in accordance with the principles of the Declaration of Helsinki. Data for each study subject were entered into a research database without patient identifiers for analysis. The study was reviewed and received ethical approval from the institutional review board.

2.3. Ventilator care bundle

A multidisciplinary team was convened to create a ventilator care bundle, which was implemented in January 2011. The ventilator care bundle consisted of five measures: (1) elevation of the patient's head from the bed to at least 30̊; (2) a structured oral care protocol, including oral care with chlorhexidine solution 0.12% every 6 h and tooth brushing with a standard toothpaste every 12 h; (3) use of cuffed endotracheal tubes when not contraindicated; (4) maintenance of tracheal tube/tracheostomy cuff pressure between 20 and 30 cmH_2O; and (5) circuit changes only if the circuit becomes soiled or damaged. In January 2012, a new tracheostomy care protocol was added. Intervals between tracheostomy tube changes increased from weekly to fortnightly, and stoma care and disinfection of the tracheostomy cannula were standardized.

All patients who underwent MV for >24 h received gastrointestinal bleeding prophylaxis. Selective digestive tract decontamination was not performed and patients did not routinely receive prophylactic antibiotics unless as surgical prophylaxis. An early, targeted antibiotic therapy for VAT was prescribed.

2.4. Educational intervention

All healthcare workers in the PICU attended an educational programme consisting of 2-h formal lectures, an educational handout, and an evaluation test before the lectures. Notices were periodically posted in the unit encouraging staff to continue applying the measures and giving feedback on the ventilator-associated infection rates. Surveys evaluating ICU staff knowledge of evidence-based guidelines for the prevention of VAP were administered twice during the study.

2.5. Statistical analysis

Descriptive data were recorded as frequencies and percentages for categorical variables. Continuous variables were expressed as the mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether the data were normally or non-normally distributed. The incidence of overall VAP, VAT, and VARI was calculated as the number of cases of VAP, VAT, and VARI per 1000 ventilator-days, either through tracheostomy or endotracheal tube. The incidence of tracheostomy VAP, VAT, and VARI was calculated as the number of cases of VAP, VAT, and VARI per 1000 tracheostomy ventilator-days. Ventilator-free days and PICU free-days at 28, 60, and 90 days were also calculated. All patients who died in the PICU had zero PICU-free days and zero ventilator-free days. Patients who were discharged on positive pressure ventilation also had zero ventilator-free days. Patients with a

baseline requirement for MV were excluded from the analysis of ventilator-free days, and patients requiring PMV were excluded from the analyses of ventilator- and PICU-free days at 28 days.

To compare study periods between groups, a Pearson Chi-square test or Fisher's exact test was used for categorical variables and the Mann–Whitney *U*-test for continuous variables. All tests were two-tailed and a *p*-value of $\leq$0.05 was considered significant. To estimate the reduction in VAP, VAT, and VARI rates between the pre- and late post-intervention periods, the relative risk (RR) and 95% confidence interval (95% CI) were calculated. For MV and PICU length of stay, as well as PICU- and ventilator-free days at 28, 60, and 90 days, the change between periods was expressed by calculating Hodges–Lehmann median differences and their 95% CI. A stepwise logistic regression model, including variables that were statistically significant in the bivariate analysis, was performed to identify independent predictors of VARI and mortality. Odds ratios (OR) and 95% CI are reported.

All analyses were performed using STATA v. 13.0 (StataCorp LP, College Station, TX, USA).

3. Results

During the study period, 312 patients (20.9%) out of 1490 admitted to the PICU underwent invasive MV for longer than 48 h. Of these, 58 patients (18.5%) were ventilated for longer than 3 weeks (PMV) and 37 were carrying a tracheostomy (11.9%). Of the 312 patients, 95 were admitted during the pre-intervention period, 109 during the early post-intervention period, and 108 during the late post-intervention period. Table 1 shows the demographic and patient characteristics. A statistically significant difference between the pre- and late post-intervention periods was found only for pre-existing respiratory conditions.

A total of 47 VARI episodes (14 VAP and 33 VAT) were documented in 37 patients. Six patients developed two or more episodes of VARI and three developed both VAP and VAT. No VAT progressed to VAP. Thirty-two VARI episodes (68%) were documented in PMV patients and 18 VARI episodes (38.3%) in patients with a tracheostomy. Overall, endotracheal, and tracheostomy VAP, VAT, and VARI rates are detailed in Table 2 and Figures 1 and 2. In the late post-intervention period, the overall VAP rate fell by 74.7% from baseline, from 4.14 to 1.05 episodes per 1000 ventilator-days (RR 0.25, 95% CI 0.04–1.18), whereas the VAP rate in tracheostomy-ventilated patients decreased from 8.16 to 0.65 cases per 1000 tracheostomy ventilator-days (RR 0.08, 95% CI 0.00–0.80). In contrast, the decline in VAT rates was not significant, either overall or in tracheostomized patients. A 2-day increase in median ventilator-free days at 28 days and an increase of more than 3 days in median PICU-free days at 28, 60, and 90 days

Table 1
Baseline characteristics of patients presenting in the pre-intervention period (2010) and follow-up periods (2011 and 2012)

	2010 (*n* = 95)	2011 (*n* = 109)	2012 (*n* =108)
Male sex, *n* (%)	55 (57.8%)	69 (63.3%)	61 (56.5%)
Age (years), mean (SD)	2.9 (4.19)	3.9 (5.09)	4.0 (5.10)
Diagnosis at admission, *n* (%)			
Surgical pathology	37 (38.9%)	40 (36.7%)	39 (36.1%)
Medical pathology	58 (62.1%)	69 (63.3%)	69 (63.9%)
Pre-existing conditions, *n* (%)			
Respiratory	4 (4.2%)[a]	8 (7.3%)[a]	18 (16.7%)[a]
Cardiovascular	40 (42.1%)	45 (41.3%)	38 (35.2%)
Neurological	3 (3.1%)	8 (7.3%)	8 (7.4%)
Renal/metabolic	2 (2.1%)	7 (6.4%)	3 (2.8%)
Gastrointestinal/liver	6 (6.3%)	8 (7.3%)	3 (2.8%)
Trauma	5 (5.3%)	1 (0.9%)	6 (5.5%)
Burn injury	2 (2.1%)	7 (6.4%)	3 (2.8%)
Immunocompromise	22 (23.1%)	17 (15.6%)	17 (15.7%)
None	21 (22.1%)	24 (22.0%)	23 (21.3%)
PELOD score, median (IQR)	13 (10–31)	13 (11–23)	12 (10.25–21)
Patients under ECMO, *n* (%)	2 (2.1%)	11 (10.1%)	9 (8.3%)
Patients with prolonged mechanical ventilation, *n* (%)	13 (13.7%)	20 (18.3%)	25 (23.1%)
Patients with tracheostomy, *n* (%)	8 (8.4%)	11 (10.1%)	18 (16.7%)

SD, standard deviation; PELOD score, Paediatric Logistic Organ Dysfunction score; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.
[a] $p < 0.05$.

Table 2
Ventilator-associated respiratory infection rates and outcomes in the pre-intervention (2010) and follow-up periods (2011 and 2012)

	2010	2011	2012	RR or between-groups difference* (95% CI)	*p*-Value
Invasive mechanical ventilation days	1451	1867	2869		
Endotracheal ventilator days (rate)	961 (0.66)	1561 (0.84)	1332 (0.46)	0.701 (0.66–0.74)	<0.001
Tracheostomy ventilator days (rate)	490 (0.34)	306 (0.16)	1537 (0.54)	1.586 (1.46–1.72)	<0.001
Overall rates[a]					
VAP, episodes (rate)	6 (4.14)	5 (2.68)	3 (1.05)	0.253 (0.041–1.184)	0.088
VAT, episodes (rate)	10 (6.89)	8 (4.12)	15 (5.23)	0.759 (0.319–1.888)	0.628
VARI, episodes (rate)	16 (11.03)	13 (6.96)	18 (6.27)	0.569 (0.274–1.193)	0.143
Endotracheal rates[b]					
VAP, episodes (rate)	2 (2.07)	4 (2.56)	2 (1.50)	0.724 (0.052–9.984)	1.000
VAT, episodes (rate)	8 (8.30)	6 (3.84)	7 (5.26)	0.633 (0.195–1.998)	0.525
VARI, episodes (rate)	10 (10.37)	10 (6.41)	9 (6.76)	0.651 (0.234–1.784)	0.476
Tracheostomy rates[c]					
VAP, episodes (rate)	4 (8.16)	1 (3.27)	1 (0.65)	0.080 (0.002–0.805)	0.028
VAT, episodes (rate)	2 (4.08)	2 (6.54)	8 (5.23)	1.275 (0.254–12.327)	1.000
VARI, episodes (rate)	6 (12.24)	3 (9.8)	9 (5.86)	0.478 (0.152–1.633)	0.262
Duration of mechanical ventilation (days), median (IQR)	7 (4–12)	7 (4–15)	6.5 (4–17.5)		0.6646
Ventilator-free days at 28 days	21 (8–24)	22 (16.5–24)	23 (19–25)	2.0 (0–3)*	0.0049
Ventilator-free days at 60 days	52.5 (0–55)	52 (36.25–56)	53 (21.75–56)	0.5 (0–2)*	0.1177
Ventilator-free days at 90 days	82 (0–85)	82 (66.25–86)	83 (50.5–86)	1.0 (0–2)*	0.1087
PICU length of stay (days), median (IQR)	11 (8–21)	14 (8–28)	9.5 (6–22.75)		0.1301
PICU-free days at 28 days	15 (0–20)	15 (7.5–20)	19 (12.5–22.5)	4.0 (1–6)*	0.0006
PICU-free days at 60 days	45 (0–52)	44 (5.25–52)	48.5 (17–54)	3.5 (0–5)*	0.0255
PICU-free days at 90 days	75 (0–82)	74 (32.75–82)	78.5 (47–84)	3.5 (0–5)*	0.0252
PICU mortality, *n* (%)	27 (28.4%)	20 (18.3%)	18 (16.7%)	0.586 (0.35–1.00)	0.062

RR, relative risk; CI, confidence interval; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; VARI, ventilator-associated respiratory infection; IQR, interquartile range; PICU, paediatric intensive care unit.
[a] Number of ventilator-associated VAP, VAT, or VARI per 1000 ventilator-days.
[b] Number of VAP, VAT, or VARI per 1000 endotracheal tube-days.
[c] Number of ventilator-associated VAP, VAT, or VARI per 1000 tracheostomy ventilator-days.

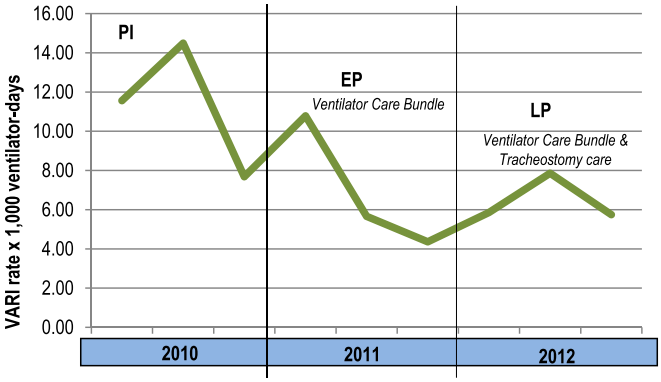

Figure 1. Overall ventilator-associated respiratory infection rates during the study period. VARI, ventilator-associated respiratory infection; PI, pre-intervention period; EP, early post-intervention period; LP, late post-intervention period.

($p < 0.05$) was observed throughout the study period. PICU mortality fell from 28.4% to 16.6% (RR 0.58, 95% CI 0.35–1.00).

Comparing VAP with VAT, the only statistically significant differences found between the groups were age (mean 21.9 months in VAT vs. 5 years in VAP; $p = 0.009$) and PICU mortality (17.4% in VAT vs. 54.5% in VAP; $p = 0.045$). There were no differences in tracheostomy, PMV, previous respiratory conditions, or ventilator- and PICU-free days.

During the study period, the median time to the development of VAT from the onset of MV or previous VARI increased significantly from 5.5 to 48 days (Table 3); however, this was not the case for VAP. Crude PICU mortality after a VARI episode was 27.6%. Gram-negative bacteria were the most common microorganisms isolated ($n = 31$, 65.9%), with *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* predominating. Seven cases of VARI (14.8%) were polymicrobial.

Comparing VARI to non-VARI patients (**Supplementary Material**, Table S1), comorbidities were less frequent in patients who did not develop a VARI. Male sex, immunocompromise, higher PELOD, PMV, and tracheostomy were more frequent in VARI patients than in non-VARI patients. In these patients, tracheostomy (OR 7.44, 95% CI 2.8–19.6) and PMV (OR 2.75, 95% CI 1.04–7.25) were the only independent risk factors associated with VARI. VARI was also significantly associated with higher mortality (35.1% vs. 16.4; $p = 0.011$). There were no statistically significant differences between groups in ventilator- and PICU-free days at 28 days, but at both 60 and 90 days there was a difference of 31 days in favour of the non-VARI group.

4. Discussion

This appears to be the first published study assessing the prevention of VAP and VAT after the implementation of a ventilator care bundle in children, including patients on PMV. Interestingly, the effect of the bundle on VAP and VAT was different. These results highlight the differences in behaviour of each ventilator-associated infection (VAT vs. VAP) according to the airway device (endotracheal vs. tracheostomy tube) and other quality-of-care indicators.

In recent years, the use of specific care bundles to control infection in the ICU has been demonstrated to be effective. Like catheter-related bloodstream infection rates, VAP rates have been proposed as a measure of a hospital's quality of care for critically ill patients. This has generated debate regarding the absence of a gold standard definition[14,15] and the exclusion of PMV patients because of the policy of discharging them to long-term care facilities.[16] Furthermore, VAT is a more frequent condition in children than VAP and is an important cause of morbidity and health resource consumption,[5–7] which is consistent with the present results. However, VAT has only rarely been considered in these studies, as have PMV patients, who are significant consumers of healthcare resources.[4] Since the prevalence of PMV in the PICU is also rising due to the increase in children with complex chronic conditions,[17] it was decided to include these patients to give a more realistic evaluation of the preventability of VARI in children.

During the study period, the number of patients with previous respiratory diseases, overall ventilator-days, and tracheostomy ventilator-days increased. Despite this rise in risk factors post-intervention,[18] it was possible to reduce the VAP rate after the implementation of the ventilator care bundle. The overall impact of

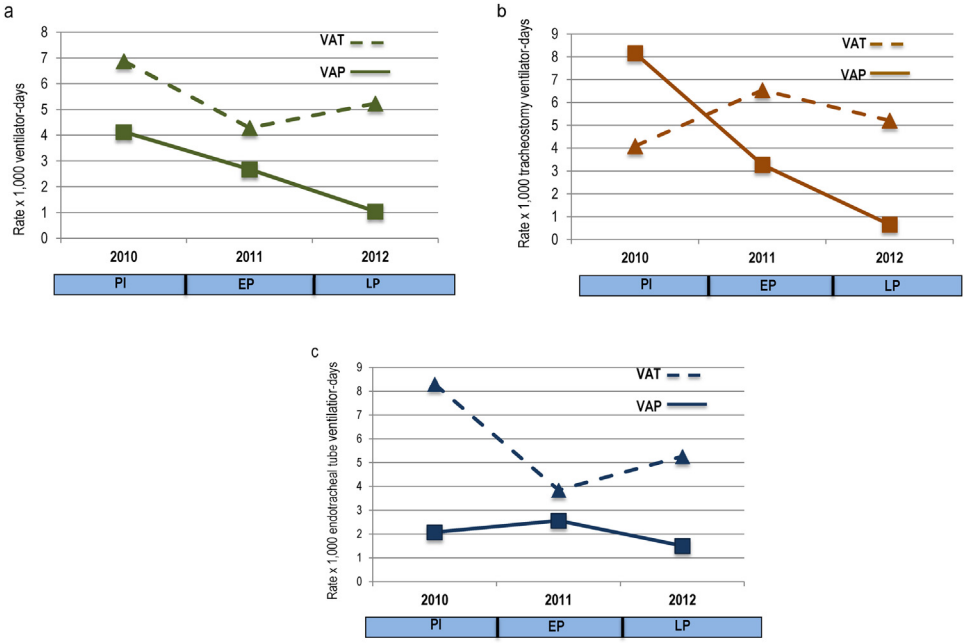

Figure 2. VAT and VAP rates: overall (a), tracheostomy (b), and endotracheal tube (c). VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia; PI, pre-intervention period; EP, early post-intervention period; LP, late post-intervention period. Dashed line = VAT rates; solid line = VAP rates.

Table 3
Median time to the development of a ventilator-associated respiratory infection from the onset of mechanical ventilation or previous episode, during the pre-intervention period and the late post-intervention period.[a]

	2010 Pre-intervention period	2012 Late post-intervention period	Between-groups difference (95% CI)	*p*-Value
Onset				
VAP	27 (9–56)	19 (4–115)	−8 (−76 to 104)	1
VAT	5.5 (2–11.5)	48 (24–93)	42.5 (3 to 65)	0.004
VARI	10.5 (3.25–32.5)	43.5 (15.5–93.5)	33 (1 to 65)	0.016

CI, confidence interval; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; VARI, ventilator-associated respiratory infection.
[a] Data are presented as the median (interquartile range).

the intervention was mostly due to a major reduction in VAP among tracheostomized patients, who represented only 11.9% of the population studied and 37.7% of MV days. Among these patients, VAP decreased by 60% after the introduction of the ventilator bundle and by a further 81% after the introduction of standardized stoma care and disinfection of the cannula. In contrast, VAP rates decreased by only 28% in patients ventilated through endotracheal tubes (275 of 312 patients, corresponding to 62.3% of MV days). This is well reflected in the fact that tracheostomy was found to be one of the significant factors associated with the development of a respiratory infection (OR 7.44, 95% CI 2.8–19.6). Until now, the role of tracheostomy as a risk factor for VAP or VAT in children has not been assessed and these are interesting data that suggest that tracheostomized children are at increased risk of ventilator respiratory infections, but that preventive measures may have a greater impact on them.

The fact that the closing of the vocal cords is preserved in most children undergoing tracheostomy, along with the difficulty in maintaining 30̊ to 45̊ head-of-bed elevation for small paediatric patients,[19] could explain the lower effectiveness of the bundle on the endotracheal tube VAP rates.

Interestingly, each of the VARI responded differently to the bundle. Both endotracheal and tracheostomy VAT rates failed to decrease significantly. These results are in contrast with those of Muszynski et al., who reported a statistically significant decrease in VAT rates after the implementation of a ventilator care bundle for preventing VAT in a PICU, although they did not include specific items for VAT.[7] The children on PMV included in the present study may explain these differences: 68% of VARI in the present series developed in patients on PMV, while the upper interquartile range of the duration of MV reported by these authors in their post-intervention period was 8.6 days. Applying a ventilator care bundle was not sufficient to significantly reduce VAT in the present study population; however, it was possible to delay the onset of VAT by 42.5 days. Thus, complete elimination of VAP and even VAT may be an unrealistic goal in a major referral hospital caring for complex patients on PMV.[9,20,21] As pointed out by Klompas, we need to consider other indicators to establish the effectiveness of the ventilator care bundle, especially in these patients.[15] Interestingly, the time to onset of VAP did not change significantly, whereas the time to onset of VAT was greatly delayed. These data suggest a different pathophysiology in VAP compared to VAT.[22] No VAP developed in patients presenting VAT, in agreement with current pathophysiological concepts that the treatment of VAT may effectively prevent VAP.[23]

The increase in median ventilator-free days and PICU-free days over the study period is also interesting, showing that the ventilator care bundle not only contributed to improved quality of care, but was also cost-saving. Considering only the cost of 1 day in the ICU (1500 Euro according to Spanish data),[20] a saving of 6000 Euro per patient and an overall saving of 648 000 Euro in days of PICU stay during the late post-intervention period was estimated. The lack of improvement in ventilator-free days at 60 and 90 days despite the increase in PICU-free days at 60 and 90 days was probably due to the fact that most PMV patients were discharged on MV. These patients, characterized by a higher burden of chronic conditions and a markedly prolonged stay, have a higher risk of VARI than others, as was shown in the present cohort and in agreement with some previous reports.[3,14,21] On the other hand, Chelluri et al. showed that while the severity of illness is the primary risk factor for death within the first 14 days of ICU admission, comorbidities are among the primary risk factors after 14 days.[24] According to the results of the present study, VARI may contribute to this. During this study, although PELOD scores were similar in the pre-intervention and post-intervention periods, overall PICU mortality dropped from 28.4% to 16.6%.

This study has several limitations. First, it was a quasi-experimental study, with a level of evidence lower than a randomized trial. The current definitions of VAP and VAT are subject to a lack of a gold standard, but they are those used by the majority of authors. Second, adherence to the bundle was not assessed, and findings might be different for other adherence rates. Some confounding clinical practices were not standardized during the study period, such as sedation, tracheostomy timing, and PICU discharge criteria, thereby limiting generalization. It is therefore possible that observed changes were caused by pre-existing secular trends or secondary to initiatives unrelated to the intervention. However, the analyses were adjusted using detailed patient-level data including age, sex, pre-existing conditions, and PELOD score. Furthermore, even if the effect on VAP and VAT was caused by something other than the intervention, the primary goal of this study was to assess the preventability of VAT and VAP when including children on PMV, rather than to test the effectiveness of the bundle per se. Additionally, this was a single-centre study, thus the results cannot be extrapolated to cohorts with a different case mix. Future research should focus on VARI instead of only VAP and should not be limited to low-risk children, but should also include tracheostomized children and those on PMV.

In conclusion, this first prospective analysis of the preventability of ventilator-associated infections in children, including those on PMV, showed that the implementation of a ventilator care bundle had different effects on VAP and VAT, diminishing VAP rates and delaying VAT onset. Furthermore, it resulted in a reduced healthcare resource use. The effect also was different depending on the airway device. Tracheostomized children were at increased risk of ventilator respiratory infections, but preventive measures had a greater impact on them.

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Conflict of interest: YP, MP, MC, AG, JAR, and JB have no conflicts of interest to disclose. JR has served on the speakers' bureau and as a consultant for Cubist, BAYER, Medimmune, Pfizer, and ARIDIS.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.09.021.

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